REMARKS/ARGUMENTS

Claims 18-23, 25 and 66-72 are currently pending in the above-identified application. Claims 66-72 have been allowed. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 18-23 and 25 in view of the remarks set forth below.

Rejections under 35 U.S.C. §101

Claims 18-23 and 25 remain rejected under 35 U.S.C. §101 as allegedly not supported by either a credible asserted utility or a well-established utility. In response to Applicants' previous arguments, mailed October 11, 2005, the Examiner states that three of the four evidentiary references cited (Heath *et al.*, Chen *et al.*, and Alexander *et al.*) have publication dates that are after the filing and priority dates of the claimed invention. (*See* Office Action dated 12/30/2005 at p. 3.) On this basis, the Examiner contends that these references cannot be relied upon "as providing proof of a well-established utility at the time the invention was made," and further asserts that "as peer-reviewed articles, these reports are assumed to provide new and original findings in the art." (*Id.*) The Examiner goes on to characterize Heath *et al.* and Alexander *et al.* and states that the instant specification "does not show ... a utility of the claimed polynucleotide commensurate" with these disclosures. (*Id.* at pp. 3 and 4.) Finally, the Examiner alleges that Staerz *et al.*, which predates the instant application, does not support a credible asserted utility for the claimed invention. (*See id.* at p. 4.) Applicants maintain traversal of the instant rejection for the reasons set forth below.

First, Applicants disagree with the Examiner's contention that the post-filing publication dates of Heath *et al.*, Chen *et al.*, and Alexander *et al.* preclude these references from being used to support a credible utility for the claimed invention. To the contrary, post-filing publications are admissible as evidence of the state of the art existing at the time the application was filed as well as evidence of operability of the invention as disclosed in the application. *Gould v. Quigg*, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987). *See also In re Hogan*, 194 USPQ 527, 537 (CCPA 1977) (stating that "[t]his court has approved the use of later filed publications as

evidence of the state of the art *existing on the filing date* of an application") (emphasis original); *In re Pottier*, 153 USPQ 407, 408 n.1 (CCPA 1967) (stating that "whether or not an invention would be deemed operative by one of ordinary skill in the art is determined, not at the time the invention was made but rather (at the earliest) at the time of the examiner's call for proof"). For reasons of record and as further set forth herein, Heath *et al.*, Chen *et al.*, and Alexander *et al.* were not submitted to supplement the disclosure in the specification but, instead, to show either (a) the knowledge in the art with respect to antigen cross-presentation as of the filing date or (b) that the invention as claimed was operable as of the filing date according to the teachings in the specification.

Further, with particular regard to the legal standard under 35 U.S.C. § 101, where a utility for a claimed invention has been asserted by the applicant, the asserted utility is sufficient if it is "credible," *i.e.*, "believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided." MPEP § 2107.02 (III)(B). "Credibility" in the context of the utility inquiry refers to the reliability of the asserted utility "based on the facts that are offered by the applicant to support the assertion of utility." *Id.* As indicated above, such facts, where relevant to the state of the art as of the filing date or operability of the invention as disclosed in the application, can be established by post-filing publications. *See Gould*, 3 USPQ2d at 1305; *Hogan*, 194 USPQ at 537; *Pottier*, 153 USPQ at 408 n.1. Moreover, evidence in support of an asserted utility need not establish the utility with absolute certainty. *See* MPEP at, *e.g.*, § 2107.03 (III) (citing *In re Woody*, 141 USPQ 518, 520 (CCPA 1964)). Indeed, rejections for alleged lack of utility have been rarely sustained by federal courts, and only then in those few cases where there was virtually no basis for an asserted utility. The MPEP states as follows:

> Rejections under 35 U.S.C. 101 have been rarely sustained by federal courts. Generally speaking, in these rare cases, the 35 U.S.C. 101 rejection was sustained either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly

> inconsistent with contemporary knowledge in the art. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967). Special care therefore should be taken when assessing the credibility of an asserted therapeutic utility for a claimed invention.

MPEP § 2107.02 (III)(B) (emphasis original).

In the present case, in view of the evidence provided by Applicants, there is no reasonable basis for maintaining that Applicants' asserted utility violates a scientific principle or a law of nature, or is wholly inconsistent with contemporary knowledge in the art. To the contrary, the totality of the evidence of record not only shows that Applicants' asserted utility is believable to a person of ordinary skill in the art, but is in fact operable according to the teachings provided in the specification. In this regard, Applicants will address the Examiner's remarks regarding each of the cited references below.

First, with respect to Heath *et al.* (*Immunol. Rev.* 199:9-26, 2004), the Examiner is referred to Applicants' previous response, in which Heath *et al.* is cited for the proposition that the "ability of exogenous antigen to be cross-presented to CTL was well-known as of the effective filing date of the instant application." (*See* Response mailed 10/11/2005 at p. 3, citing Heath *et al.* at p. 11, bridging to p. 12.) Applicants' citation to Heath at fn.5 specifically notes that pre-filing date references are cited by Heath *et al.* Thus, Heath *et al.* is used in this context as evidence of the state of the art as of the effective filing date of the application, and can therefore be relied upon to at least this extent. *See, e.g., Gould*, 3 USPQ2d at 1305; *Hogan*, 194 USPQ at 537.

Furthermore, Heath *et al.* can also be relied upon insofar as it supports operability of the claimed invention as disclosed in the application. *See, e.g., Gould*, 3 USPQ2d at 1305; *Pottier*, 153 USPQ at 408 n.1. In this respect, Applicants again note that Heath *et al.* states that MHC class I-restricted presentation of both endogenous and exogenous sources of antigen can occur. (*See* Heath *et al.* at p. 10, first col., last paragraph, bridging to second col.) This statement directly rebuts the Examiner's allegation that exogenous antigen cannot be presented

by MHC class-I molecules. Accordingly, to the extent that the Examiner relies on this allegation as a basis for contending that the claimed invention is inoperable, Heath *et al.* is relevant and admissible as evidence of operability of the claimed invention.

The Examiner also states that "Heath discloses that some antigen presenting cells can 'cross-present' peptide antigens from other cells from the subject that were apoptotic or phagocytosed by the antigen presenting cells." (*See* Office Action dated 12/30/05 at p. 3, last para.) Applicants agree that Heath discusses the uptake of apoptotic cells as one mechanism for access to the cross-presentation pathway. Heath also discloses, however, other targets for cross-presentation, including soluble antigens. (*See* Heath *et al.* at, *e.g.*, p. 11, 1st col. bridging to 2nd col.; and p. 13, 1st col., top of 1st full para. (both citing, *e.g.*, Staerz *et al.*, which predates the application.) In this regard, Applicants note that the application, in the context of using peptides of the invention for immunization, discloses that the peptides can be administered to an individual as, *e.g.*, a solution. (*See* specification at, *e.g.*, p. 24, ll. 25-29.)

The Examiner goes on to state that Heath *et al.* discusses "DNA vaccination" using sequences encoding peptides into muscle cells and subsequent capture of the expressed peptides by APC. (*See* Office Action dated 12/30/05 at p. 3.) The Examiner then goes on to state that "the present specification does not disclose the use of the claimed polynucleotides to transfect cells other than the APCs for take up of the expressed peptide ...." (*Id.* at p. 3, bridging to p. 4) In response, while Applicants acknowledge that Heath *et al.* contains some discussion regarding DNA vaccination, Applicants have not cited Heath *et al.* to support a utility that necessarily relies on DNA vaccination. As set forth above, Heath *et al.* is cited in support of the fact that CTL-inducing peptides themselves can be taken up and presented via an exogenous pathway. Further, any discussion in Heath *et al.* pertaining to DNA vaccination does not contradict the statements in the reference to the effect that class I peptide epitopes can be presented via an exogenous pathway. Therefore, since only one credible asserted utility is required to satisfy utility under § 101, Applicants believe that the Examiner's remarks regarding DNA vaccination to be largely irrelevant to the issue at hand.

With respect to Chen & Jondal (*Scand. J. Immunol.* 59:545-552, 2004), again, the Examiner is referred to Applicants' previous response, in which Chen is cited for the proposition that while intracellular proteins are processed to form MHC class-I binding peptides, "***most*** CTL responses are probably initiated by the uptake of exogenous antigens into DC in a process called 'cross-priming.'" (*See* Response mailed 10/11/2005 at p. 4., citing Chen & Jondal at p. 545, first col. (emphasis provided).) This statement by Chen is relevant to operability of the claimed invention as disclosed in the application. The present specification discloses that "pan DR peptides are useful as an adjuvant component ... to enhance an immune response against an administered antigen," including when "conjugated with a CTL-inducing peptide ... to induce a CTL response." (*See* specification at p. 10, ll. 5-12.) If most CTL response are initiated by the uptake of exogenous antigens, as evidenced by Chen, then Applicants' assertion regarding the usefulness of the claimed peptides upon administration to a subject is more likely true. Chen is therefore relevant to operability of the invention as disclosed in the application. Accordingly, because post-filing publications relevant to operability of a disclosed invention are admissible, *see Gould,* 3 USPQ2d at 1305; *Pottier*, 153 USPQ at 408 n.1, Chen is properly relied upon by Applicants.

With regard to Alexander *et al.* (*J. Immunol.* 168:6189-6198, 2002), the Examiner states that this publication "discloses naked DNA vaccination of muscle tissue for expression of immunogenic peptides, which allowed APC to capture, process, and present antigenic peptide in context of MHC class I." (Office Action dated 12/30/05 at p. 4.) The Examiner then goes on to state that "the present specification does not disclose the use of the claimed polynucleotides to transfect cells other than the APCs for take up of the expressed peptide ...." (*Id.*) In response, these statements do not address Applicants' citation to Alexander *et al.* as describing the use of multideterminant ***peptides*** containing a pan DR epitope covalently linked to one or more CTL epitopes." While Applicants acknowledge that Alexander *et al.* contains some discussion regarding DNA vaccination, most of this reference is directed to studies showing induction of immune responses by administration of the peptides. Further, as with Heath *et al.*, Applicants have not cited Alexander *et al.* to support a utility that necessarily relies on DNA vaccination,

and Alexander's discussion regarding DNA vaccination does not contradict Alexander's actual demonstration that a pan-DR binding peptide linked to a CTL peptide is itself useful for inducing an immune response. Accordingly, as only one credible asserted utility is required to satisfy utility under § 101, Applicants believe that the Examiner's remarks regarding DNA vaccination to be irrelevant to the outstanding issue in this case.

What is particularly relevant is that Alexander demonstrates induction of an immune response with peptides according to the teachings of the present specification. The specification teaches, *inter alia*, fusion proteins comprising at least one pan DR-binding peptide comprising AKFVAAWTLKAAA (SEQ ID NO:22) and at least one CTL-inducing peptide, as presently recited in the claims. The specification further discloses that peptides comprising a pan DR-binding peptide conjugated to a CTL-inducing peptide can be administered to induce a CTL response. (*See* specification at, *e.g.*, p. 10, ll. 10-12.) In Alexander, the pan DR-binding epitope (PADRE®) used has the sequence AKFVAAWTLKAAA and is thus the same as that presently recited in the claims. (*See* Alexander *et al.* at, *e.g.*, p. 6190, Table I.) This epitope was added to varying number of CTL epitopes to yield a panel of deca-, hexa-, tetra-, tri-, and bi-epitope constructs comprising PADRE®. (*See id.* at p. 6193, 2nd col., first full para.; and p. 6194, Figure 5.) These peptides were used as immunogens for administration to HLA transgenic mice. (*See id.* at, *e.g.*, p. 6194, Figure 5 (legend).) *Ex vivo* and *in vitro* recall $CD8^+$ (CTL) and $CD4^+$ (HTL) responses were primed using each of the peptides. (*See id.* at p. 6193, 2nd col., 2nd full para.)

Thus, Alexander shows that peptides as disclosed and claimed in the specification are indeed operable in a manner commensurate with at least one asserted utility. Again, because post-filing publications relevant to operability of a disclosed invention are admissible, *see Gould,* 3 USPQ2d at 1305; *Pottier*, 153 USPQ at 408 n.1, Alexander is properly relied upon by Applicants.

With regard to Staerz *et al.* (*Nature* 329:449-451, 1987), the Examiner states that "while the CTLs were able to react when primed with soluble ovalbumin, they were only able to do so in the presence of CNBr-fragmented ovalbumin." (Office Action dated 12/30/05 at p. 4.) If, by this statement, the Examiner means to suggest that Staerz does not demonstrate uptake,

processing, and presentation of MHC class-I antigens via an exogenous pathway, Applicants disagree. To further clarify the Staerz reference, Applicants note that mice were immunized with soluble ovalbumin, *i.e.*, with exogenous antigen. (*See* Staerz *et al.* at 450, 1st col.) Accordingly, the presence (in cells from immunized mice) of antigen-specific lytic activity restricted by MHC class I molecules would demonstrate that CTLs had been primed *in vivo* with antigen taken up, processed, and presented via an exogenous pathway. The presence of such lytic activity was demonstrated in Staerz *et al.* by the *in vitro* CML assays, using spleen cells from the immunized mice. (*See* Staerz *et al.* at p. 450, Figure 1.)

Specifically, *in vitro* cultures were tested for lytic activity on tumor cell targets in the presence of ovalbumin fragmented with either trypsin or CNBr. (*See* Staerz at p. 450, Figure 1 (see legend: panels *a* and *b* correspond to trypsin digested ovalbumin, while panel *c* corresponds to CNBr-fragmented ovalbumin.) Thus, fragments of ovalbumin are loaded onto MHC class I molecules expressed by the targets. These assays were, therefore, not designed to test for uptake and processing of exogenous antigen by the target cells. Instead, the assays were designed to confirm whether exogenous antigen uptake, processing, and presentation to CTLs had occurred during *in vivo* immunization, as indicated by a lytic response against the antigen-loaded targets by CTLs from immunized mice.

The CML assays indeed confirmed successful *in vivo* priming with exogenous antigen. Targets cells syngeneic to the immunized mice (and therefore expressing the same MHC haplotype) were used. (*See* Staerz *et al.* at p. 450, 1st col. (bottom).) As would be expected for an MHC-restricted response, immunization did not result in appreciable lytic activity toward allogeneic targets (expressing different MHC haplotypes) in the presence of fragmented ovalbumin, but a specific response was mounted against the syngeneic targets in the presence of fragmented ovalbumin. (*See id.* at p. 450, 1st col., bridging to 2nd col.)

Applicants also disagree with the Examiner's reliance on the statement that "Staerz also showed that CTL were able to kill EL4 tumor cells that had been transfected with ovalbumin, but not EL4 cells that had taken up exogenous antigen." (Office Action dated 12/30/2005 at p. 4, 2nd para.) Again, it is noted that the CML assays were designed to test for

the ability of CTLs from immunized mice to recognize ovalbumin epitopes expressed by fragmentation. Such recognition, as measured by lytic activity, could only occur if the immunization with exogenous antigen resulted in successful processing and presentation to CTLs *in vivo*. In the case of transfected EL4 cells, the transfection was used as a means to test whether CTLs from immunized mice could also recognize epitopes "expressed not only by chemical and enzymatic fragmentation, but intracellular protein degradation." (*See* Staerz *et al.* at p. 450, 2nd col., 2nd full para.) Thus, the fact that an immune response was mounted against transfected EL4 cells actually confirmed successful CTL priming *in vivo* with exogenous antigen. The use of undigested ovalbumin in this particular assay was merely used to control for the possibility that CTLs were recognizing epitopes from ovalbumin secreted from and taken up by EL4 cells. (*See id.*)

Moreover, as noted in Applicants' previous response, Staerz *et al.* specifically conclude from their data that exogenous antigen can be presented via the MHC class I pathway:

> As it is clear from our data that at least part of the activity induced by our immunization protocols is carried out by conventional CTL recognizing epitopes found on ovalbumin, there ***cannot*** be a complete separation of the two pathways of antigen presentation for MHC class I-restricted and MHC class II-restricted antigens. Our data indicate the existence of a mechanism allowing ***exogenous*** antigens to be presented in conjunction with MHC class I molecules in a similar way to antigens expressed within the cell.

(Staerz *et al.* at p. 451, 1st col. (top).) Applicants note that, to the extent the Examiner suggests that Staerz *et al.* do not demonstrate processing and presentation of exogenous antigen in the context of MHC class I, the Examiner attempts to interpret the Staerz data in a way that directly contradicts the authors' own conclusions. The Examiner, however, has not presented any evidence that one of skill in the art would reach a conclusion different than that reached by the authors' themselves.

In light of the above, the references previously submitted by Applicants are properly relied upon and admissible to support a credible asserted or well-established utility

under 35 U.S.C. § 101. The Examiner has failed to evaluate all relevant evidence of record and has not made a *prima facie* showing of no specific and substantial credible utility, *i.e.*, "that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant." MPEP § 2107.02 (IV). The evidence of record clearly establishes that the asserted utility is not only credible, but is in fact well-documented by those of skill in the art at the time of filing. Moreover, the evidence confirms that the peptides of the invention, as disclosed and claimed in the application, are in fact operable in a manner commensurate with Applicants' asserted utility. Based on the totality of evidence and reasoning provided herein and in Applicants' previous response, claims 18-23 and 25 comply with the utility requirement under 35 U.S.C. § 101. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 18-23 and 25 remain rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification. On the basis of an alleged lack of utility for claims 18-23 and 25 as set forth in the Examiner's rejection under 35 U.S.C. § 101, the Examiner contends that one skilled in the art would not know how to use the claimed invention.

Applicants maintain traversal of the instant rejection. For the reasons discussed in response to the rejection under 35 U.S.C. § 101, claims 18-23 and 25 are supported by a credible or well-established utility. Accordingly, the skilled artisan would know how to use the invention as claimed. Withdrawal of the rejection is respectfully requested.

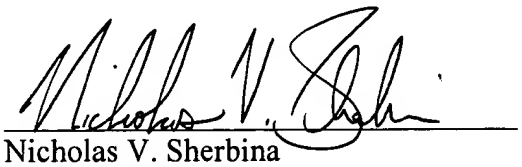
CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Date: June 28, 2006

By: 

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